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Brain Natriuretic Peptide and the Risk of Cardiovascular Events and Death in Patients with Atrial Fibrillation

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1. Introduction

Brain natriuretic peptide (BNP) is a hormone that is secreted by the heart, especially from the ventricle (Sudoh et al., 1988; Yasue et al., 1994). The plasma BNP concentrations (BNP levels) are correlated positively with the left ventricular end-diastolic pressure and negatively with the left ventricular ejection fraction (Yoshimura et al., 1993; Maeda et al., 1998), so BNP levels should be measured to evaluate left ventricular function. BNP levels have proved to be good markers of congestive heart failure. In addition, BNP levels are useful in screening test for left ventricular dysfunction and also heart disease.

Some studies have shown that BNP levels have a prognostic value of mortality and morbidity in patients with chronic heart failure (Maeda et al., 2000; Anand et al., 2003), in general populations (Wang et al., 2004) and in clinical practice (Tsuchida & Tanabe, 2008). However, the prognostic value of BNP levels in patients with atrial fibrillation (AF) is not well known. This study investigated the relations of BNP levels to cardiovascular events and death in patients with AF.

Hohnloser et al. suggested that warfarin therapy was needed in patients with paroxysmal AF similarly as in those with sustained AF (Hohnloser et al., 2007). Another report showed that, if sinus rhythm was maintained with antiarrhythmic therapy, the prognosis of the patients with paroxysmal AF for ischemic stroke was better than those with permanent AF (Komatsu et al., 2004). We examined the necessity of warfarin therapy in patients with paroxysmal AF as in those with chronic AF.

Furthermore, CHADS₂ score is known to be very useful to decide the indication of warfarin therapy in patients with AF (Gage et al., 2001). The patients with CHADS₂ score of 2 or more are recommended to take warfarin therapy, those with CHADS₂ score of 1 to take Warfarin or antiplatelet drugs, and those with CHADS₂ score of 0 need not any take warfarin. We investigated the usefulness of BNP as an aid in CHADS₂ score to decide the indication of warfarin therapy in patients with CHADS₂ score of 0 or 1.

2. Subjects and methods

2.1 Subjects

This study included 371 consecutive outpatients with AF in the Tsuchida Clinic of Internal Medicine and Cardiology (23-93 years with an average age of 69.5±10.8 years; 205 men and

166 women; 231 paroxysmal AF and 140 chronic AF), whose BNP levels were measured to evaluate left ventricular function from 1999 to 2002. The patients were treated according to the relevant guidelines and followed up until 31 December 2006. The mean follow-up period was 5.4 years (max: 7.5 years). Diagnosis was based on history, physical examination, laboratory findings, chest X-rays, electrocardiograms and echocardiograms. Paroxysmal AF was defined as AF that terminated spontaneously within 7 days after onset. Chronic AF was defined clinically when defibrillation of paroxysmal AF was unsuccessful (permanent AF) or AF was continuously observed for more than 6 months (persistent AF).

2.2 Methods

BNP levels were measured by the immunoradiometric assay method using a Shionoria BNP assay kit (Shionogi, Osaka, Japan) for the one-point blood sample taken in a sitting position. Some studies of patients with heart failure (Latini et al., 2004; Tsutamoto et al., 1997) showed that BNP levels of more than about 100 pg/ml were significantly related to mortality and morbidity, so the patients were stratified into two groups based on cut-off levels of BNP (<100 pg/ml and ≥ 100 pg/ml).

The primary endpoint was a composite of cardiovascular events (hospitalization and death). Components of the endpoints included the following: heart failure, coronary heart disease events (acute myocardial infarction, unstable angina), stroke (ischemic, hemorrhagic), arrhythmia, dissecting aneurysm, peripheral arterial disease, infective endocarditis, acute myocarditis, renal infarction, pulmonary infarction, embolism of the superior mesenteric artery, and sudden cardiac death. The first of these events was noted as the primary event. Any component of a composite primary endpoint, for which a patient could be counted once in each category, was treated as a second endpoint. Death from any cause was also designated a secondary endpoint. Furthermore, patients with paroxysmal AF were observed for the development of chronic AF. The study protocol was approved by the Ethics Committee of Tsuchida Clinic of Internal Medicine and Cardiology.

2.3 Statistical analysis

Values are shown as mean \pm standard deviation (SD). Time-to-event curves for the endpoints were estimated by the Kaplan-Meier method for the entire follow-up period. The log-rank test was used to examine the association of BNP levels. Hazard ratio (HR) and 95% confidence interval (CI) were calculated and adjusted for age, sex, the presence or absence of hypertension, diabetes mellitus, and hyperlipidemia with the Cox's proportional hazards model. All analyses were performed with the use of StatView (version 5.0). Significance levels were $p < 0.05$ in these analyses.

3. Results

3.1 Patient characteristics

Clinical characteristics are summarized in Table 1. This study included 371 patients: valvular disease was found in 57 (15%); congestive heart failure (CHF) in 58 (16%); coronary artery disease (CAD) in 47 (13%), old myocardial infarction (OMI) in 16 (4%), angina pectoris (ANG) in 31 (8%); prior stroke in 35 (9%); hypertrophic cardiomyopathy (HCM) in 19 (5%); dilated cardiomyopathy (DCM) in 10 (3%); prior pacemaker operation in 12 (3%); hypertension in 228 (62%); diabetes mellitus in 63 (17%); dyslipidemia in 104 (28%); including some patients with more than one disease. In comparing chronic AF with paroxysmal AF, there were more valvular disease, CHF, and prior stroke in patients with

	All	PAF	CAF	p Value
	(n=371)	(n=231)	(n=140)	
Age (years)	69.5±10.8	68.4±10.9	71.3±10.2	0.0119
Male gender	205 (55%)	121 (52%)	84 (60%)	0.1534
BNP (pg/ml)	96	57	160	<0.0001
Cardiovascular disease				
Valvular disease	57 (15%)	22 (10%)	35 (25%)	<0.0001
CHF	58 (16%)	12 (5%)	46 (33%)	<0.0001
CAD	47 (13%)	16 (7%)	13 (9%)	0.1925
OMI	16 (4%)	11 (5%)	5 (4%)	0.5855
ANG	31 (8%)	5 (3%)	8 (6%)	0.1531
Prior stroke	35 (9%)	15 (7%)	20 (14%)	0.0127
HCM	19 (5%)	10 (4%)	9 (6%)	0.3752
DCM	10 (3%)	2 (1%)	8 (6%)	0.0127
Prior pacemaker operation	12 (3%)	4 (2%)	8 (6%)	0.0356
Hypertension	228 (62%)	147 (64%)	81 (58%)	0.2688
Diabetes mellitus	63 (17%)	33 (14%)	30 (21%)	0.0760
Dyslipidemia	104 (28%)	70 (30%)	34 (24%)	0.2121
CHADS ₂ score	1.43	1.23	1.76	<0.0001
0	82 (22%)	60 (26%)	22 (16%)	
1	138 (37%)	95 (41%)	43 (31%)	
2	86 (23%)	46 (20%)	40 (29%)	
3	38 (10%)	21 (9%)	17 (12%)	
4-6	27 (7%)	9 (4%)	18 (13%)	
Medication				
Warfarin	90 (24%)	38 (17%)	52 (37%)	<0.0001
Antiplatelet drugs	177 (48%)	99 (43%)	78 (56%)	0.0162
Beta-blocker	24 (7%)	20 (9%)	4 (3%)	0.0277
ACEI/ARB	55 (15%)	40 (17%)	15 (11%)	0.1033
Ca blocker	196 (53%)	128 (55%)	68 (49%)	0.2018
Digitalis	270 (73%)	173 (75%)	97 (69%)	0.2408
Antiarrhythmic drugs	77 (21%)	65 (28%)	12 (9%)	<0.0001
Thiazide	72 (19%)	25 (11%)	47 (34%)	<0.0001
Antialdosterone agents	60 (16%)	20 (9%)	40 (29%)	<0.0001
Nitrates	27 (7%)	17 (7%)	10 (7%)	0.9382
Statins	95 (26%)	60 (26%)	35 (25%)	0.8355

* PAF: paroxymal atrial fibrillation, CAF: chronic atrial fibrillation
* ACE: angiotension converting enzyme inhibitor, ARB: angiotensin receptor blocker

Table 1. Characteristics of the Study Population

chronic AF than in those with paroxysmal AF. And BNP levels in patients with chronic AF (160 pg/ml) were about 3 folds compared to with paroxysmal AF (57 pg/ml, during sinus rhythm). Patients with chronic AF had a mean CHADS₂ score of 1.76 compared with 1.23 in those with paroxysmal AF (p<0.0001). The reason for the higher mean CHADS₂ score in patients

with chronic AF was probably because of older age, the presence of more structural heart disease (valvular disease, DCM, prior pacemaker operation and CHF) and prior stroke. The prior use of warfarin, wntiplatelet drugs, beta-blocker, thiazide and antialdosterone drugs was significantly higher in chronic AF. And the prior use of antiarrhythmic drugs was significantly higher in paroxysmal AF.

3.2 Kaplan-Meier curves for the endpoints and Incidence of death or cardiovascular events

Patients were stratified into two groups based on cut-off level of BNP (100 pg/ml), and a cumulative cardiovascular event-free curve was constructed according to Kaplan-Meier analysis. Cumulative cardiovascular event-free rate, as evaluated by Kaplan-Meier analysis, was significantly lower with a BNP level \geq 100 pg/ml ($p<0.0001$) (Figure 1). Similarly, in secondary analyses (cardiovascular mortality, all-cause mortality, heart failure, ischemic stroke, development of paroxysmal AF into chronic AF), cumulative survival rate (event-free rate) was significantly lower with a BNP level \geq 100 pg/ml (Figure 2, Figure 3, Figure4, Figure 5, Figure 6). But only with regard to coronary heart disease events, the cumulative event-free rate was not significantly associated with the BNP level.

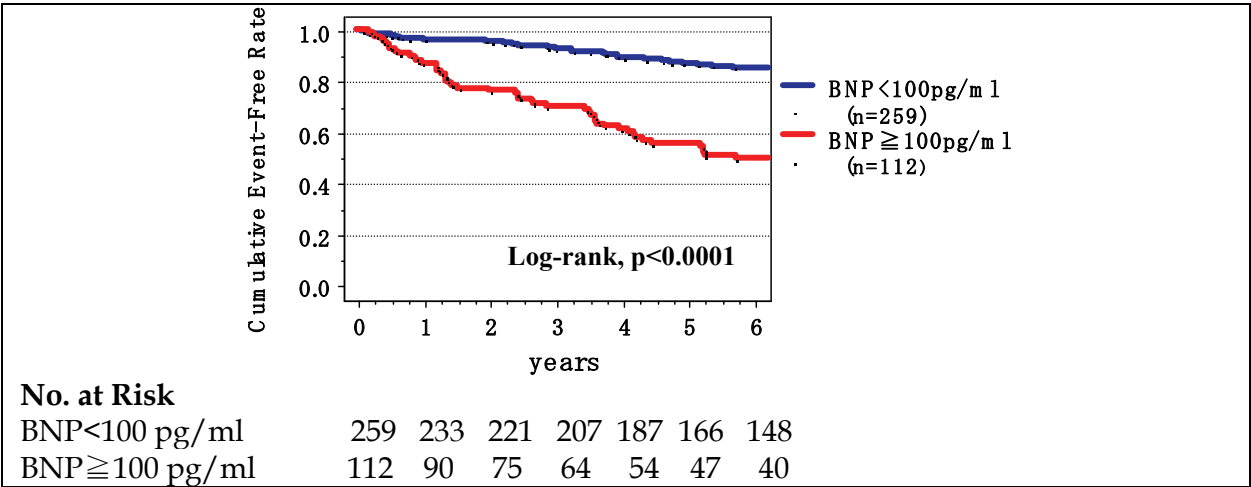


Fig. 1. Kaplan-Meier Curve for Cardiovascular Events

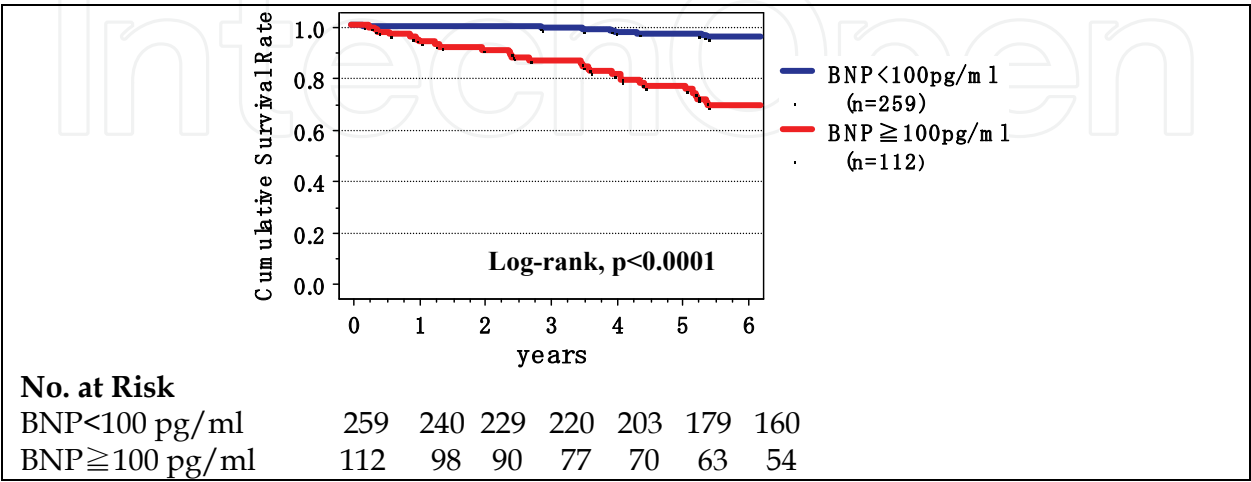


Fig. 2. Kaplan-Meier Curve for Cardiovascular Mortality

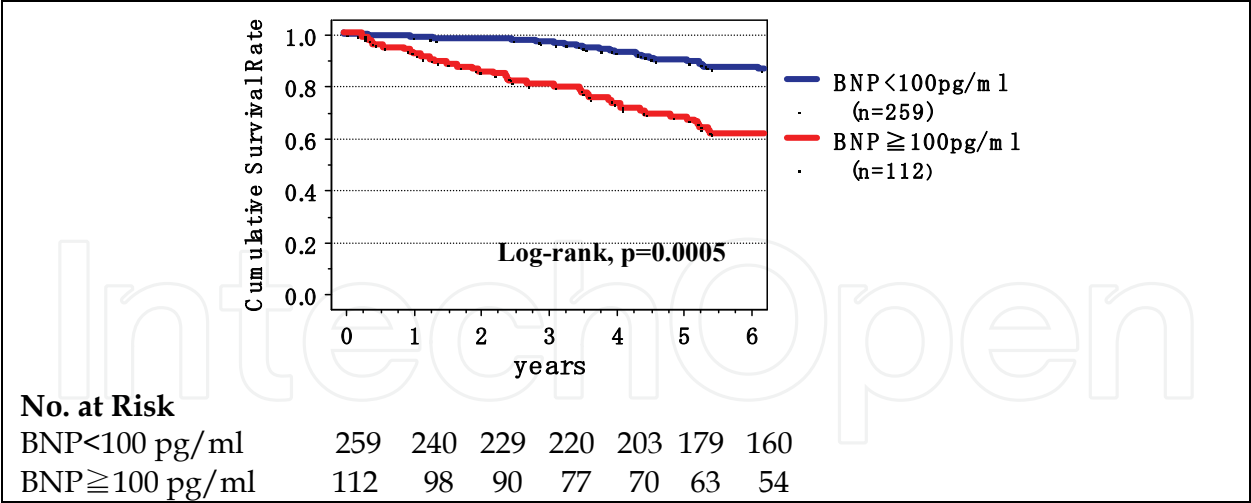


Fig. 3. Kaplan-Meier Curve for All-Cause Mortality

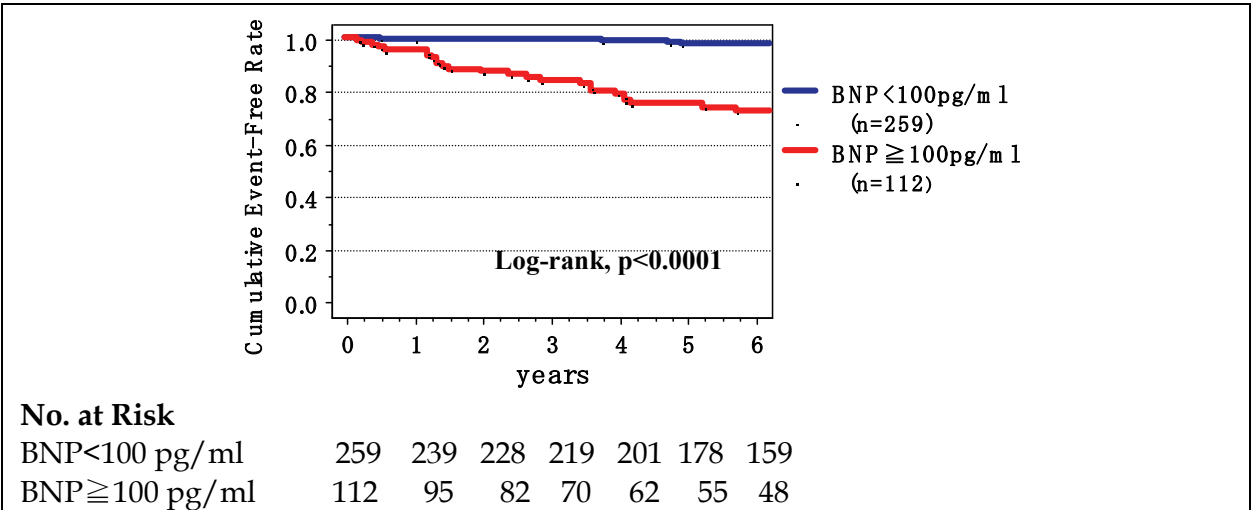


Fig. 4. Kaplan-Meier Curve for Heart Failure

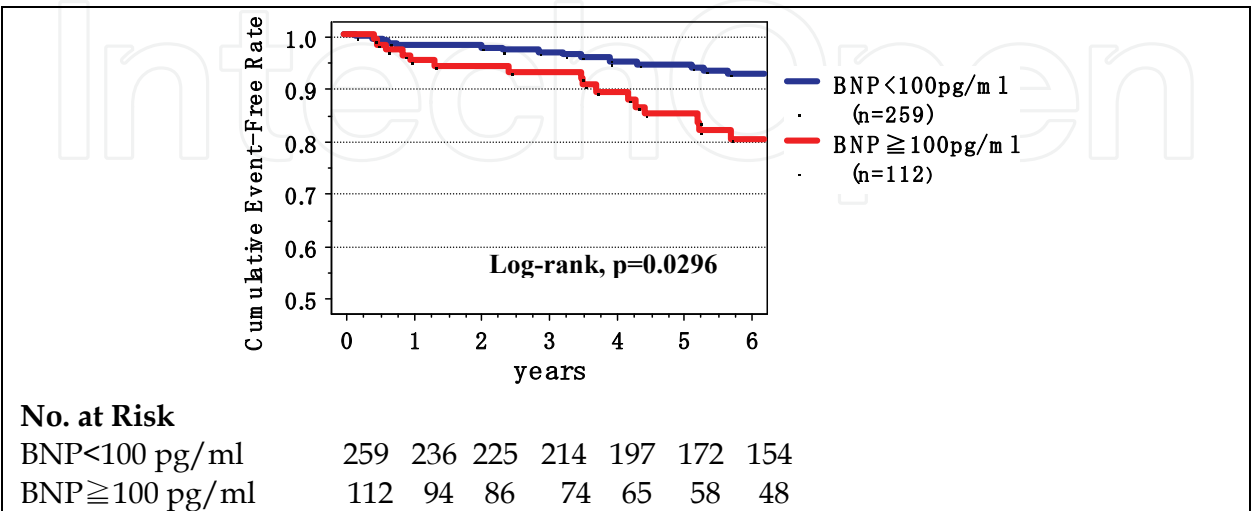


Fig. 5. Kaplan-Meier Curve for Ischemic Stroke

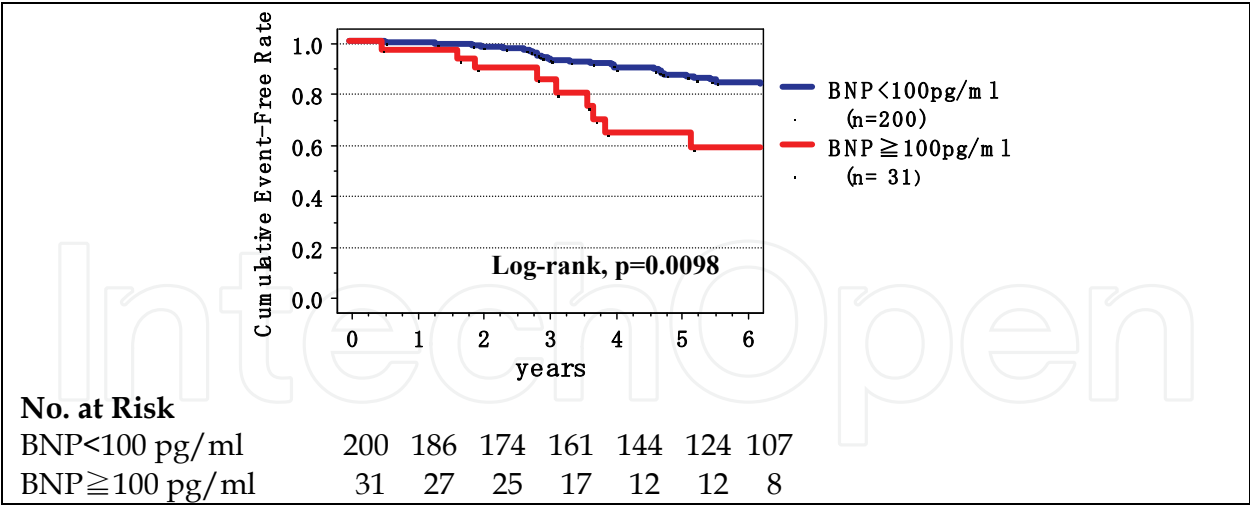


Fig. 6. Kaplan-Meier Curve for Development of Paroxysmal AF into Chronic AF

	Number of events		HR (95%CI)	p Value
	BNP ≥100	BNP<100		
	(n=112)	(n=259)		
Primary endpoint				
Cardiovascular events	58 (52%)	38 (15%)	3.9 (2.6-6.0)	<0.0001
Secondary endpoints				
Cadiovascular mortality	35 (31%)	11 (4%)	5.2 (2.6-10.5)	<0.0001
All-cause mortality	47 (42%)	33 (13%)	2.3 (1.4-3.7)	0.0005
Heart failure	30 (27%)	8 (3%)	11.0 (4.9-24.5)	<0.0001
Coronary h.d. events	2 (2%)	4 (2%)	0.9 (0.1-5.3)	0.8840
Ischemic stroke	19 (17%)	18 (7%)	2.1 (1.1-4.1)	0.0296
Development of PAF into CAF (PAF, n=231)	10/31 (32%)	29/200 (15%)	2.8 (1.3-6.1)	0.0098

Table 2. Incidence of Cardiovascular Events in Patients with AF

During a mean follow-up of 5.4 years, the number of cardiovascular events was 96/371 (26%): heart failure 38, coronary heart disease events 6 (acute myocardial infarction 6), stroke 38 (ischemic 37, hemorrhagic 1), arrhythmia 7 (sick sinus syndrome 4, atrioventricular block 1, ventricular tachycardia 1), embolism of superior mesenteric artery 1, renal infarction 1, others 5. The number of deaths from cardiovascular disease was 46/371 (12%): heart failure 17, coronary heart disease events 2 (acute myocardial infarction 2), stroke 17 (ischemic 16, hemorrhagic 1), arrhythmia 2 (ventricular fibrillation 2), embolism of superior mesenteric artery 2, dissecting aneurysm 1, others 5. The number of deaths from all causes was 80/371 (22%): cardiovascular disease 46 (as was stated above), malignant tumor 20 (lung 4, stomach 3, colon 5, pancreas 3, esophagus 2, others 3), pneumonia and chronic obstructive pulmonary disease 3, renal failure 2, liver cirrhosis 2, others 7.

A BNP level≥100 pg/ml was associated with a HR (95% CI) of 3.94 (2.57-6.04) for cardiovascular events compared with a BNP<100 pg/ml (p<0.0001), 5.18 (2.55-10.52) for

cardiovascular mortality ($p<0.0001$), 2.32 (1.44-3.72) for all-cause mortality ($p=0.0005$), 11.01 (4.94-24.54) for heart failure ($p<0.0001$), 2.11 (1.08-4.14) for ischemic stroke ($p=0.0247$) , 2.80 (1.28-6.10) for development of paroxysmal AF into chronic AF ($p=0.0098$); however, it was 0.87 (0.14-5.34) for coronary heart disease events ($p=0.8840$). In addition, paroxysmal AF developed into chronic AF in 39 of 231 patients (16.9%, 3.1% of patients per year).

3.3 Incidence of stroke in patients with paroxysmal AF and chronic AF

Furthermore, the incidence of ischemic stroke was significantly with $BNP\geq 100$ pg/ml than with $BNP<100$ pg/ml (HR: 5.31, 95%CI: 1.49-18.89, $p=0.0812$) by univariate analysis (Figure 8), whereas in patients with chronic AF, it was not significantly associated with the BNP levels (HR: 1.02, 95% CI: 0.48-2.18, $p=0.3623$) (Figure 9).

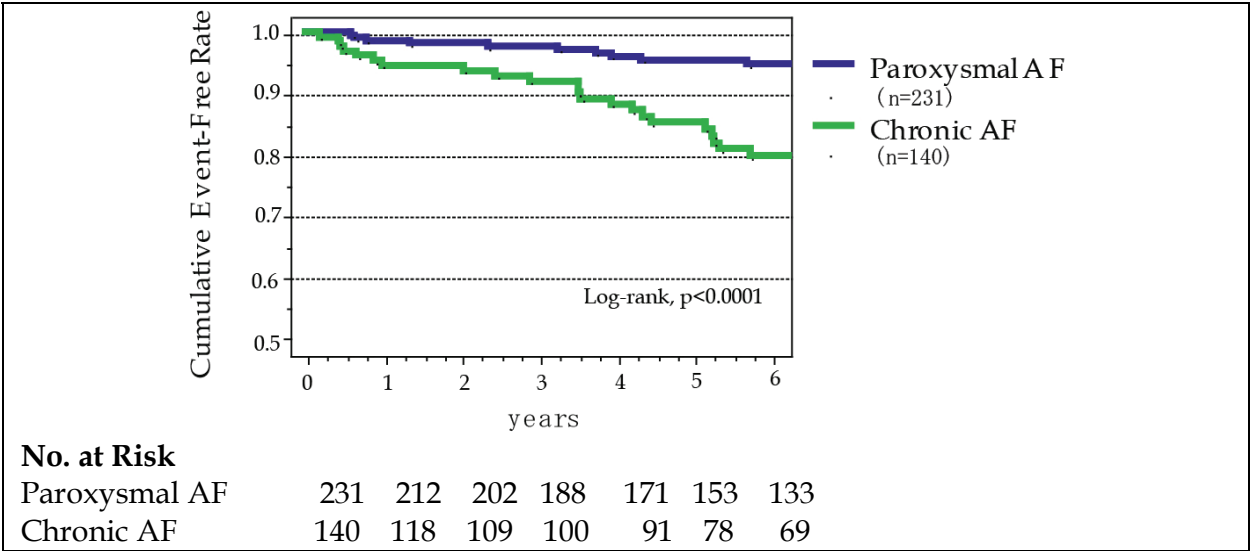


Fig. 7. Kaplan-Meier Curve for Ischemic Stroke in Patients with paroxysmal AF and chronic AF

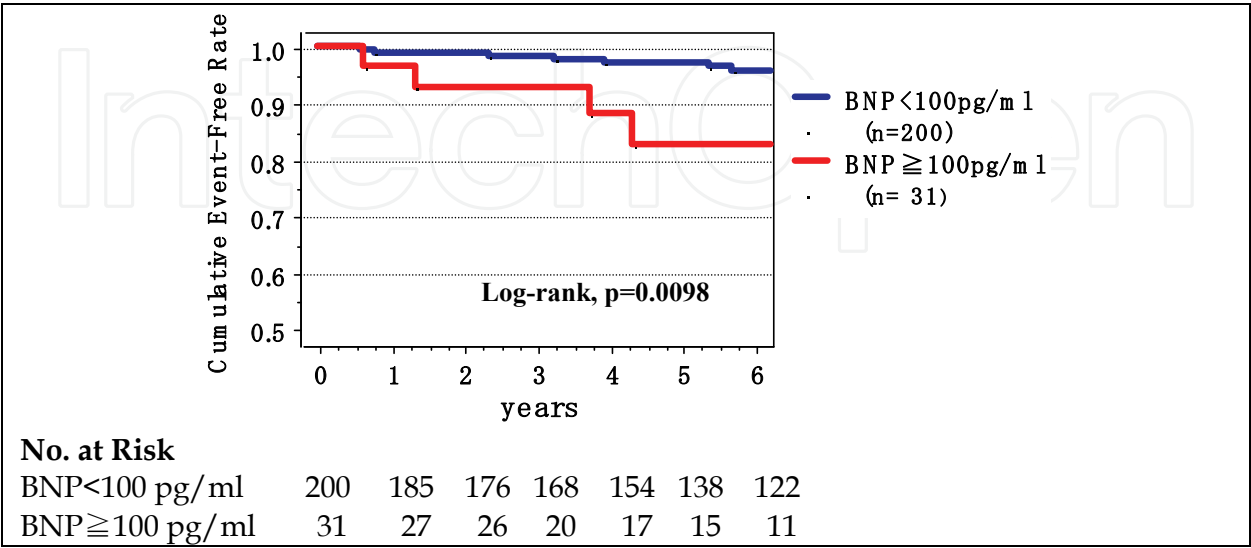


Fig. 8. Kaplan-Meier Curve for Ischemic Stroke in Patients with Paroxysmal AF

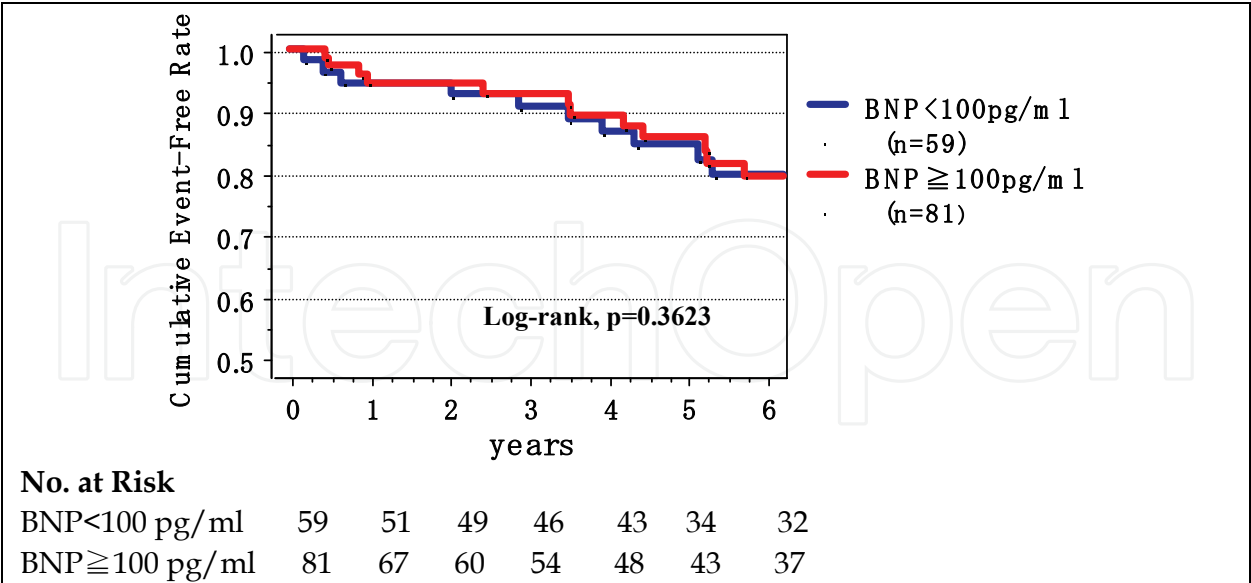


Fig. 9. Kaplan-Meier Curve for Ischemic Stroke in Patients with Chronic AF

3.4 CHADS₂ Score and Incidence of Ischemic stroke

Based on Kaplan-Meier analysis of five groups stratified by CHADS₂ score (0, 1, 2, 3, 4-6) in Figure 10, it was found that as CHADS₂ score was higher, the cumulative event-free rate for ischemic stroke decreased significantly (p<0.0001). As detailed in Table 3, there was the number of prior use of warfarin and the incidence of ischemic stroke, stratified by CHADS₂ score.

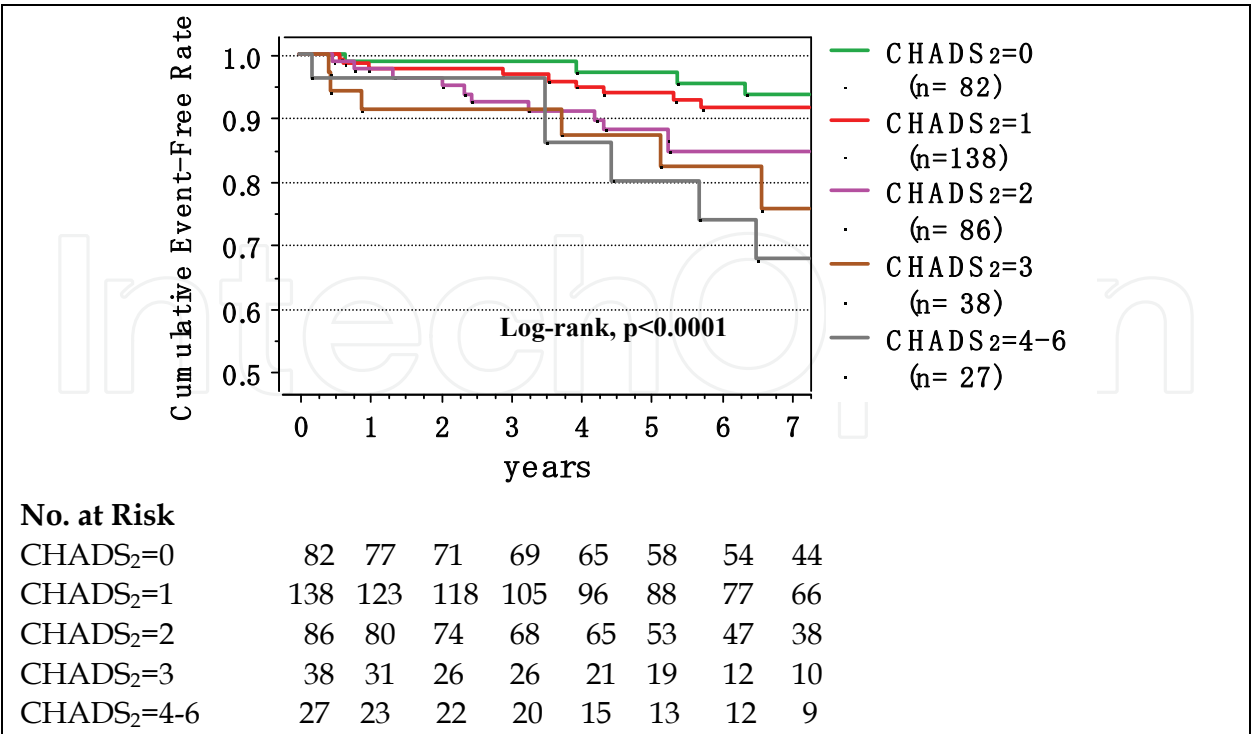


Fig. 10. Kaplan-Meier Curve for Ischemic Stroke, Stratified by CHADS₂ Score

CHADS ₂ score	No. of patients (n=371)	Prior use of warfarin (n=90)	No. of stroke (n=37)
0	82	16 (20%)	3 (4%)
1	138	25 (18%)	9 (7%)
2	86	25 (29%)	13 (15%)
3	38	10 (26%)	6 (16%)
4-6	27	14 (52%)	6 (22%)

Table 3. Incidence of Stroke and Prior Use of Warfarin, Stratified by CHADS₂ Score

In patients with CHADS₂ score of 0 or 1, a BNP level ≥ 100 pg/ml was associated with a HR (95% CI) of 3.84 (1.18-12.47) for ischemic stroke compared with a BNP < 100 pg/ml (p=0.0254) (Figure 11).

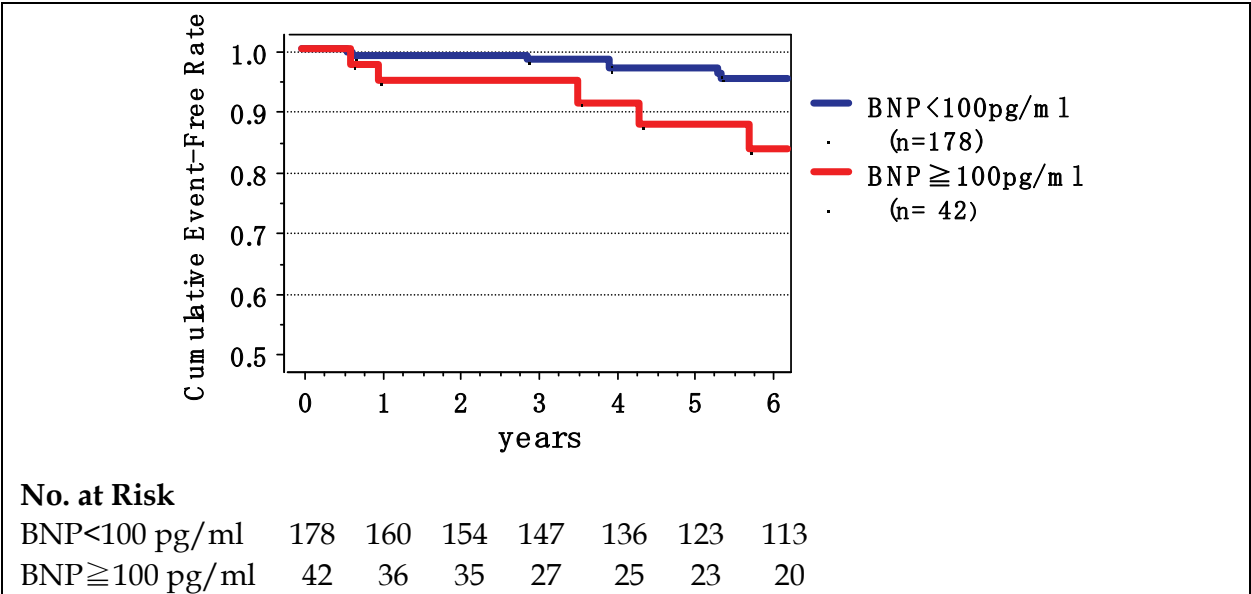


Fig. 11. Kaplan-Meier Curve for Ischemic Stroke in Patients with CHADS₂ Score of 0 or 1

4. Discussion

4.1 BNP and the risk of cardiovascular events and death in patients with AF

BNP is a hormone that is secreted by the heart, especially from the ventricle (Sudoh et al., 1988; Yasue et al., 1994), and BNP levels are useful in diagnosis and screening for left ventricular dysfunction and heart failure. Furthermore, during AF, BNP was known to be secreted mainly from the atrium in response to atrial wall stretch (Inoue et al., 2000). Our previous study in outpatients with paroxysmal AF showed that BNP levels during AF attack were increased 2.4 times compared with BNP levels during sinus rhythm (SR) (Tsuchida & Tanabe, 2004). Another study on electric defibrillation in patients with chronic AF showed an increase of about three times during AF than during SR after electric defibrillation (Ohta et al., 2001). These studies revealed that BNP levels during AF (both paroxysmal AF attack and chronic AF) are 2-3 times higher compared to during SR, and therefore BNP level during AF is the sum of the BNP level from the ventricle (reflecting left ventricular function) and the atrium (due to atrial wall stress).

Some studies have shown that BNP levels have a prognostic value of mortality and morbidity in patients with chronic heart failure (Maeda et al., 2000; Anand et al., 2003), in general populations (Wang et al., 2004) and in clinical practice (Tsuchida & Tanabe, 2008). This study shows that BNP level in patients with AF is an important prognostic marker of cardiovascular events, cardiovascular mortality, all-cause mortality, heart failure, ischemic stroke and development of paroxysmal AF into chronic AF, by stratification into two groups based on routinely used cut-off levels of BNP (100pg/ml).

The 14 year follow-up study of paroxysmal AF (Kato T et al., 2004) revealed that paroxysmal AF eventually developed into chronic AF in 132 of 171 patients (77.2%, 5.5% of patients per year), despite changing the drugs as necessary, and the development ratio was significantly increased by aging, an enlarged left atrium, myocardial infarction and valvular disease. In this study (5.4 year follow-up), paroxysmal AF developed into chronic AF in 39 of 231 patients (16.9%, 3.1% of patients per year), and the development ratio was significantly higher in patients with a $\text{BNP} \geq 100$ pg/ml than a $\text{BNP} < 100$ pg/ml. It is conceivable that the reason for lower development ratio in this study than in the former study, is because of less myocardial infarction (5% in this study versus 11% in the former study) and valvular disease (10% versus 20%).

In patients with coronary heart disease, BNP levels were definitely associated with acute phase and outcome of myocardial infarction (Morita et al., 1993; Bibbins-Domingo et al., 2003; Morrow et al., 2003; Suzuki et al., 2004). However, in this study, we did not find an association between BNP levels and the risk of coronary heart disease events in patients with AF, reflecting a similar finding in the report of the Framingham study in a community-based population (Wang et al., 2004).

4.2 Incidence of stroke in patients with paroxysmal AF and chronic AF

Hohnloser et al. (2001) suggested that Warfarin therapy was needed in patients with paroxysmal AF, similarly as in those with sustained AF (Hohnloser et al., 2007). Meanwhile, another study showed that, if SR was maintained with antiarrhythmic therapy, the prognosis of the patients with paroxysmal AF for ischemic stroke was better than those with permanent AF (Komatsu et al., 2004). In this study, the incidence of ischemic stroke was significantly higher in patients with chronic AF than in those with paroxysmal AF. The reason for it was because of older age, the presence of more structural disease (valvular disease, DCM, prior pacemaker operation and CHF), more prior stroke and higher mean CHADS₂ score in patients with chronic AF.

This study showed that the incidence of ischemic stroke was significantly higher with a $\text{BNP} \geq 100$ pg/ml than with a $\text{BNP} < 100$ pg/ml. In addition, in patients with paroxysmal AF, the incidence of ischemic stroke was significantly higher with a $\text{BNP} \geq 100$ pg/ml than with a $\text{BNP} < 100$ pg/ml, whereas in patients with chronic AF, it was not significantly associated with the BNP levels.

In our previous study (Tsuchida & Tanabe, 2004), BNP levels during AF attack in patients with paroxysmal AF are 2.4 times higher (due to atrial wall stretch) compared to during SR, and even an asymptomatic AF attack also showed substantial and significant BNP elevation (median BNP levels: 31 pg/ml during SR, 71 pg/ml during AF attack). These findings suggest that BNP elevation of unknown origin could be attributed to the occurrence of asymptomatic AF attack, and the incidence of AF attack may be higher in paroxysmal AF patients with a $\text{BNP} \geq 100$ pg/ml, besides the degree of left ventricular dysfunction.

Furthermore, in this study, the incidence of development of paroxysmal AF into chronic AF was significantly higher with a $\text{BNP} \geq 100$ pg/ml, and so paroxysmal AF with a $\text{BNP} \geq 100$ pg/ml may be going to develop close to chronic AF.

As to the mechanism of association between elevation of BNP levels and development of ischemic stroke in AF patients, there are a few reports. The recent studies demonstrated that BNP levels correlated negatively with left atrial appendage flow velocity in chronic AF patient, and suggested that pathological changes (such as hypertrophy, fibrosis and inflammation) in the atrial myocardium may also be underlying factors in elevated BNP secretion in patients with poor left atrial appendage function, and so BNP as a reflection of left atrial appendage function may be a useful marker to predict vulnerability to thromboembolism in AF patients (Frustaci et al., 1997; Shimizu et al., 2002). Further study needs to be performed as to the mechanism of association between elevation of BNP levels and development of ischemic stroke in AF patients.

4.3 Warfarin therapy in patients with CHADS₂ score of 0 or 1

CHADS₂ score is known to be very useful to decide the indication of warfarin therapy in patients with AF (Gage et al., 2001). The patients with CHADS₂ score of 2 or more are recommended to take warfarin therapy, those with CHADS₂ score of 1 to take warfarin or antiplatelet drugs, and those with CHADS₂ score of 0 need not take any warfarin.

Based on Kaplan-Meier analysis of five groups stratified by CHADS₂ score (0, 1, 2, 3, 4-6), it was found that as CHADS₂ score was higher, the cumulative event-free rate for ischemic stroke decreased significantly. Furthermore, in the patients with CHADS₂ score of 0 or 1, the incidence of ischemic stroke was significantly higher with a $\text{BNP} \geq 100$ pg/ml than with a $\text{BNP} < 100$ pg/ml. So in the patients with CHADS₂ score of 0 or 1, BNP may be useful as an aid in CHADS₂ score to decide the indication of warfarin therapy for prevention to ischemic stroke.

4.4 Study limitations

The study population consisted of 371 outpatients of one local clinic in Japan. Although they were treated according to the accepted guidelines, it was unavoidable that this study showed a certain amount of bias in relation to patient background, diagnosis and treatment.

5. Conclusion

In patients with AF, BNP levels predicted the risk of cardiovascular events and death, except for coronary heart disease. Patients with chronic AF had a higher risk of ischemic stroke than patients with paroxysmal AF. BNP may be useful as an aid in CHADS₂ score to decide the indication of warfarin therapy in patients with paroxysmal AF and in patients with CHADS₂ score of 0 or 1.

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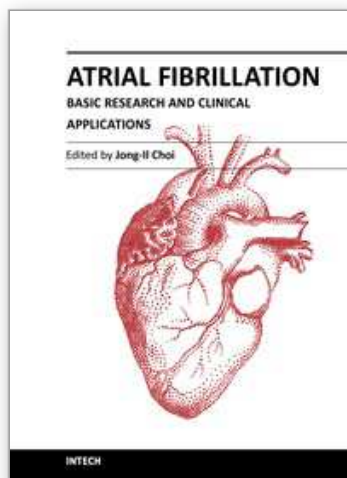
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